Patent Application
Docket No. INN.123
Serial No. 10/537,394

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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|---|---|---|
| Examiner | : | Marcos L. Sznaidman |
| Art Unit | : | 1612 |
| Applicants | : | Francois Romagne, Helene Sicard, Jerome Tiollier, Christian Belmant |
| Serial No. | : | 10/537,394 |
| Filed | : | June 2, 2005 |
| For | : | Compositions and Methods for Regulating an Immune Response in a Subject |

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF FRANCOIS ROMAGNE, HELENE SICARD, JEROME TIOLLIER AND CHRISTIAN BELMANT UNDER 37 C.F.R. §1.131

Sir:

Francois Romagne, Helene Sicard, Jerome Tiollier and Christian Belmant declare:

1. That we are co-inventors of the invention disclosed and claimed in U.S. Application Serial No. 10/537,394;

2. That said invention was conceived and reduced to practice on, or before, July 8, 2002 (the critical date) in France;

3. That we conceived and reduced to practice methods for treating methods of treating solid tumors and cancers, such as renal cell carcinoma, using the claimed compounds, such as 3-(bromomethyl)-3-butanol-1-yl-diphosphate (BrHPP) to induce γδ T-cells in and individual having a solid tumor or cancer; and

4. That Exhibit 1 contains a copy of a document establishing that the inventors conceived of a method of treating a solid tumors comprising the administration of a composition γδ cell activator, such as BrHPP, in a pharmaceutically acceptable carrier and administering such a composition to a subject having a solid tumor or cancer (e.g., renal cell carcinoma). Dates and other confidential information have been redacted from the attached exhibit; however, the document and was prepared on or prior to the critical date of July 8, 2002.

We hereby further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Further, Declarants sayeth not.

By: _____ Date: May 19 2009
Francois Romangne

By: _____ Date: 7th May 09.
Helene Sicard

By: _____ Date: May 19, 2009
Jerome Tollier

By: _____ Date: 07 - May - 2009
Christian Belmant

Attachment: Exhibit 1; Laboratory data

# EXHIBIT 1

# 1 INTRODUCTION

## *1.1 Project Identification*

**PROGRAM : Phosphohalohydrins (PHD)**

**TITLE :** "Feasibility of the pharmaceutical development of a phosphohalohydrin compound for cancer immuno-therapy "

**SHORT TITLE :** PHD program / validation phase

**PHASE : RESEARCH STAGE PROJECT / VALIDATION (R1)**

## *1.2 Project summary*

The researches of J.J.Fournié & M. Bonneville have led to the identification of several γ9δ2-stimulating compounds, isolated from microbial and parasite sources. These molecules turned out to be small molecular weight (MW< 500), non-peptidic phosphorylated compounds. They selectively stimulate the proliferation and the effector responses of human γ9δ2-T lymphocytes in short term culture of peripheral blood lymphocytes drawn from healthy donors. In addition to an IL2-dependent proliferation, these responses, which can also be detected with γ9δ2-T cell clones stimulated in vitro, include a very rapid cytokine release (*i.e.* TNF-α and -β, γ-IFN) and induced cytotoxicity towards a broad spectrum of tumor cell targets.

Microbial phosphoantigens are highly bioactive compounds ($EC_{50}$: ~5 nM), but they are quite difficult to isolate from natural sources, and are quite unstable. Hence these research teams have designed and synthesized agonists of equal or higher bioactivity than the natural phosphoantigens: the phosphohalohydrins (PHD, e.g. bromohydrin BrHPP, iodohydrin IHPP and chlorahydrin ClHPP) and the phosphoepoxides (PED).These compounds have a much higher chemical stability than the natural homologues in physiological conditions, and a remarkably simple synthesis procedure. Preliminary in vivo studies conducted in academic laboratories suggest that BrHPP should be devoid of major acute toxicity, and that activation of γ9δ2 cells is observed in primates treated with repeated doses of BrHPP. Other compounds than the PHD/PED were synthesized, but their activity was weaker than that of the group of four PHD/PED molecules. The compounds of interest appear on figure 1 and nomenclature in table below. All four compounds tested were synthetized at the mg scale by C.Belmant in J.J.Fournié's laboratory prior to the initiation of the project.

Innate Pharma has acquired [redacted] PHD and PED patents [redacted] and intends to develop one of this compound as a pharmaceutical product for cancer immuno-therapy based on the activation of γ9δ2 effector cells. The therapeutic product may either be a drug for systemic administration to cancer patients or a cellular therapy process consisting of the administration of ex-vivo activated cells using a PHD/PED compound plus IL-2.

### *1.3 Objectives and acceptance criteria*

With respect to the aims defined in project summary [redacted], several aspects will be addressed :

**Chemistry** : the main objective is to obtain the informations required for the transfer of the project to a CPM which would be in charge of GMP manufacturing and DMF filing and therefore to assess :

(i) feasibility of the synthesis of each compound at the gram scale at 'reasonable cost'
(ii) feasibility of an analytical methods for each selected compound, based on standard industry practices such as ES-MS.
(iii) Identification of major impurities

**Pharmaceutical properties** : It is not in the scope of the feasibility study to design the formulation of the drug product, nor to test the stability of the drug substance. However, preliminary studies will be conducted to determine whether the compound(s) of interest can be sterilized by heat, lyophilized, and to measure stability of standard formulation in liquid/solid forms so as to identify the main mechanisms of product degradation.

**Toxicology** : preliminary acute toxicology studies will be performed in mice iv. Genotoxicity will also be assessed by in vitro predictive methods (Ames test ; micronucleus assay, UDS). Predictive toxicology is based on receptor profiling.

**Pharmacology** : The main objectives are :

(i) to confirm the active doses in a battery of in vitro assays
(ii) to assess in vitro response to PHD+IL-2 in cancer patients (patient responsiveness)
(iii) to assess tumor sensitivity to γ9δ2 lysis using battery of relevant cell lines for various tumor histological types
(iv) to provide evidence for a significant biological response to PHD when injected systemically in responding animals such as primates or SCID mice populated with human γ9δ2 cells

| **Study** | **Acceptance criteria (go / no go AND compound selection)** |
|---|---|
| Chemistry / synthesis | Gram scale synthesis feasible ; [redacted] |
| Chemistry / analytical | Method for product analysis ; sensitivity < 1 µM |
| Chemistry / analytical | Major impurities identified |
| Stability | No evidence of degradation for one month in stressed conditions for at least one tested formulation |
| Genotoxicity | No detectable genotoxicity (non cancer indications) / acceptable genotoxicity from expert point of view (cancer indications) |
| Receptor profiling | No significant binding with a panel of relevant receptors |
| Acute toxicology | DL50 > 100mg/kg ; No significant organ toxicity |
| In vitro pharmacology | ED50 < 100 nM using various readouts |
| In vitro pharmacology | >50% cancer patient responsive to PHD+IL-2 in selected indication |
| In vitro pharmacology | >80% cell lines killed by PHD-activated cells in selected indication |
| In vivo pharmacology | Significant biological response in animals injected with compound |

The feasibility study aims at :

(i) [redacted] pharmaceutical development of the group of compound either as drugs or as ancillary product for cellular therapy for a cancer indication ,

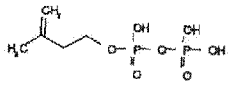
(ii) selecting the compound of interest for further development among the four products BrHPP, ClHPP, IHPP and EpoxPP

(iii) providing a rationale for activation of γ9δ2 effector cells as a therapeutic approach in cancer immuno-therapy.

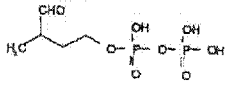
Taken together, these three questions lead to the first development milestone for the company, designated as 'milestone M1' in the business plan.

| Compound | Acronym | Product code |
|---|---|---|
| **Phosphohalohydrines (PHD)** | | |
| IodoHydrine PyroPhosphate | IHPP | [redacted] (batch number) |
| BromoHydrine PyroPhosphate | BrHPP | [redacted] (batch number) |
| ChloroHydrine PyroPhosphate | ClHPP | [redacted] (batch number) |
| **Phosphoepoxides (PED)** | | |
| Epoxyde PyroPhosphate | EpoxPP | [redacted] (batch number) |

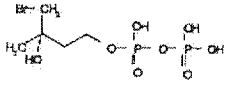
**IHPP**
Isopentenyl pyrophosphate *(10-30 µM)*



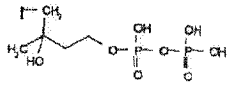
Phosphoantigène mycobactérien
*(10-30 nM)*



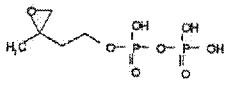
**BrHPP**
Bromohydrin pyrophosphate *(10 nM)*



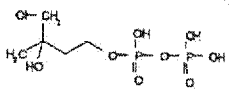
**IHPP**
Iodohydrin pyrophosphate *(1 nM)*



**EpoxPP or PED**
Epoxide pyrophosphate *(20 nM)*



**ClHPP**
Chlorohydrin pyrophosphate *(100 nM*



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4. THAT, the BioNews press release cited in the obviousness rejection in this matter was prepared by one or more employees of Innate Pharma, the assignee of this matter;

5. THAT, the information contained in the BioBews press release originated, or was obtained/derived, from us during the course of a discussion, or discussions, between us and the individual(s) at Innate Pharma responsible for the preparation of the press release; and

6. THAT, the author(s) and publisher(s) of the BioNews press release did not conceive of, or invent, the subject matter disclosed in the press release.

We hereby further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Further, Declarants sayeth not.

By: _____ Date: May 13. 2009
Francois Romangne

By: _____ Date: 7th May 2009
Helene Sicard

By: _____ Date: May 7 2009
Jerome Tollier

By: _____ Date: 07 May 2009
Christian Belmant